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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			HA, JULIE	
			ART UNIT	PAPER NUMBER
			1654	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/529,203	<b>Applicant(s)</b> BAUER ET AL.	
	<b>Examiner</b> JULIE HA	<b>Art Unit</b> 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 01 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1, 10, 12-14, 16-18, 26, 27, 29, 30, 32-38, 40-58 and 60 is/are pending in the application.
- 4a) Of the above claim(s) 50-54 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 10, 12-14, 16-18, 25-27, 29-30, 32-38, 40-49, 55-58 and 60 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/12/2007</u> .  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 01, 2008 has been entered. Claims 2-9, 11, 15, 19-24, 28, 31, 39 and 59 have been cancelled. Claims 1, 10, 12-14, 16-18, 26-27, 29-30, 32-38, 40-58 and 60 are pending in this application. Claims 50-54 remain withdrawn from further consideration as being drawn to nonelected invention. Claims 1, 10, 12-14, 16-18, 25-27, 29-30, 32-38, 40-49, 55-58 and 60 are examined on the merits in this office action.

### ***Withdrawn Rejection***

3. Rejection of claims 1-2, 4, 8-10, 12-14, 16-18, 27, 33, 36-37, 43-49 and 55-57 under 35 U.S.C. 102(b) is hereby withdrawn due to Applicant's amendment to the claims.

### ***Maintained Rejection-35 U.S.C. 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 10, 12-14, 16-18, 25-27, 29-30, 32-37, 43-49 and 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gefter et al (US Patent # 6180608) in view of Bauer et al (PG Pub 2002/039996).

8. Gefter et al teach pharmaceutical compositions comprising a stable water-insoluble complex composed of a peptidic compound, preferably a pharmaceutically active peptidic compound, and a carrier macromolecule that allows for sustained delivery of the peptidic compound in vivo upon administration of the complex. The reference further teaches that the complex can permit continuous delivery of a

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pharmaceutically active peptidic compound to a subject for prolonged periods of time, e.g., one month, two months, three months and the like (see column 1, lines 43-52 and column 6, lines 12-13). Furthermore, the reference teaches that the complex is formed by combining the peptidic compound and the carrier macromolecule under conditions such that a substantially water-insoluble complex is formed, e.g., aqueous solutions of the peptidic compound and carrier macromolecule are mixed until the complex precipitates. The complex may be in the form of a solid (e.g., a paste, granules, a powder or a lyophilisate)...can be pulverized finely enough to form stable liquid suspensions or semi-solid dispersions (see column 1, lines 57-65). This reads on claim 33 and claim 36 in part. The reference further teaches that the peptidic compound of the water-insoluble complex is an LHRH analog, and LHRH antagonist (see column 1, lines 66-67 and column 2, line 1). Furthermore, the reference teaches that the complex is suitable for sterilization, such as by gamma irradiation or electron beam irradiation, prior to administration in vivo (see column 2, lines 3-5). This reads on claims 36 and 37. Further, the reference teaches a method for treating a subject for a condition (prostate cancer) treatable with an LHRH analog by administering to the subject an LHRH-analog-containing composition (see column 2, lines 6-11). This reads on claims 48-49. The LHRH analogs are LHRH antagonists, and include antide, Cetrorelix and the like (see column 4, lines 6-27). The reference further discloses that multivalent cationic peptidic compound and multivalent anionic peptidic compound refer to peptidic compound comprising a multiplicity of positive or negative charges (see column 3, lines 46-49). Furthermore, the reference teaches that the pharmaceutical formulations

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comprise additional pharmaceutically acceptable carriers and/or excipients...the carrier is suitable for intravenous, intramuscular, subcutaneous or parenteral administration (e.g., by injection) (see column 7, lines 65-67 and column 8, lines 1-7). This reads on claim 43. The reference further teaches that a non-limiting range of an LHRH analog is 0.01 mg to 10 mg/kg (see column 10, lines 37-38) and Examples 2-4 disclose 25 mg of peptidic compound dissolved in water (Example 2), 50 mg of peptidic compound dissolved in mannitol and carboxymethylcellulose (Example 3) and 25 mg of peptidic compound dissolved in water and added to sodium alginate (Example 4). This reads on claims 16-18. The reference further teaches that the reconstitution vehicle to be used in clinical studies is 0.9% sodium chloride (see Example 14). This reads on claims 12-14 and 27. The difference between the reference and the instant claims are that the reference does not teach D-63153, and additionally pharmaceutically active ionic peptide compound and differing NaCl concentrations.

9. However, Bauer et al disclose a pharmaceutical administration forms suitable for parenteral administration, which contains peptides prone to aggregation in the form of their acetate, gluconate, glucuronate, lactate, citrate, ascorbate, benzoate, or phosphate salts in dissolved or dispersed form (see abstract). Furthermore, the reference discloses that the pharmaceutical administration forms can be present in dissolved or dispersed form in water or in aqueous solvent mixtures (see paragraph [0012]). Additionally, the reference discloses that the peptides employed are LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrotorelix, antarelix and the antagonists according to the U.S. Patent # 5942493 and DE 19911771.3. (see

paragraph [0014] and US Patent No. 7,005,418, column 3, lines 53-58). D-63153 is an antagonist disclosed in DE 19911771.3. Furthermore, the reference discloses that preparation of sterile solutions of LHRH antagonist for parenteral administration is by means of filtration, especially at high concentration (see paragraph [0009]). Additionally, the reference discloses that the administration of pharmaceutically active peptides is the parenteral pharmaceutical form...in the form of reconstituted lyophilisates of soluble peptide salts and to microparticles, microcapsules or implants (see paragraph [0010]). Furthermore, the reference discloses that area of use of the preparations is in the prevention and therapy of all sex hormone-dependent conditions and diseases, which can be influenced by LHRH agonist and antagonists...benign prostate hyperplasia, carcinoma of the prostate, precocious puberty, hirsutism, endometrial hyperplasia, uterine myomatosis, breast cancer, etc (see paragraphs [0020] and [0021] and claims 16 and 17). Furthermore, the reference discloses rat animal experiment (see paragraph [0041] and Tables 8a, 8b and 9). Please note that the reference discloses the disorders that are claimed in claims 50-53 of instant application.

10. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Gefter et al and Bauer et al because both prior arts teach pharmaceutical gel formulation incorporating GnRH antagonist. There is a motivation to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist and one would expect the same activity. There is a reasonable expectation of success to substitute D-63153 for other GnRH antagonist, since both prior arts disclose Antide and Cetrorelix as examples of GnRH antagonists that can be formulated

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into composition in an aqueous solvent. Further, there is a reasonable expectation of success since 0.9% sodium chloride is used to reconstitute for clinical studies (see Example 14 of patent '608) and sustained delivery formulation for administering pharmaceutically active peptides in vivo continuously for prolonged time periods are achieved by patent '608. The references are silent as to the range of NaCl concentrations.

11. However, the MPEP states the following: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.

*"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."* In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 (*"The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."*); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the



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criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Therefore, there is a reasonable expectation of success to optimize the NaCl concentration, since “*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*” One of ordinary skill in the art would have been motivated to optimize the NaCl range with for the expected benefit of at least increasing the clinical utility of the pharmaceutical preparation.

12. Furthermore, the MPEP states the following: “It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in

cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant."). Therefore, there is a reasonable expectation of success to add in another pharmaceutically active ionic peptide compound in a pharmaceutical gel preparation comprising D-63153, since the above mentioned compounds (such as cetorelix) are all GnRH antagonist that are used for the same purpose, thus addition of another GnRH antagonist would at least have an additive effect.

### ***Response to Applicant's Arguments***

13. Applicant argues that "in Gefter et al, the carrier macromolecule comprises cationic carrier macromolecule like poly-L-lysine and other polymers of basic amino acids or anionic carrier macromolecule like polyalcohol derivatives...The current invention does not comprise a carrier macromolecule and does not use such carrier macromolecule. On the contrary the inventive peptide forms the administration form for sustained release itself." Applicant further argues that "Gefter et al use a 0.9% sodium

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chloride in Example 14 as a reconstitution vehicle to reconstitute the complex PPI-149-CMC, consisting of the peptidic compound PPI-149 and the macromolecule carboxymethylcellulose, wherein the complex PPI-149 is already a sustained delivery complex. However, the present invention uses sodium chloride as an inorganic salt as the reconstitution medium and to prepare a sustained release form from an easily soluble peptide or peptide salt." Further, Applicant argues that "Bauer et al does not actually disclose or suggest D-63153. U.S. Patent No. 5,942,493 and DE 19911771.3 references disclose a large number of peptides, one of which is D-63153. However, Bauer et al or these references fail to provide any specific motivation to select D-63153 for use as presently claimed." Further, Applicant argues that "the Examiner offers nothing to show how the KSR factors apply and how the results set forth in the Examples of the present application would be expected or anticipated success."

14. Applicant's arguments have been fully considered but have not been found persuasive. Gefter et al teach the GnRH (LHRH) antagonist such antide and cetrorelix and a carrier molecule for sustained release *in vivo*. In regards to Applicant's argument that instant invention "does not comprise a carrier macromolecule and does not use such carrier macromolecule", Applicant is reminded that the claim recites the transitional phrase "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps (see MPEP 2111.03). Therefore, other elements may be included in the claimed language. Further, Gefter reference teaches the reconstitution of the GnRH antagonist in 0.9% NaCl for clinical utility. Since the sustained release form of PPI-149 is being reconstituted in the same NaCl solution, this

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meets the limitation of the claims. Bauer reference teaches that pharmaceutically active decapeptides (cetrorelix) in the form of their pharmaceutically acceptable, non-toxic acid addition salts such as hydrochlorides...acetates, citrates...etc (see paragraph [0002]). Further, Bauer discloses pharmaceutical administration forms suitable for parenteral administration, which contains peptides prone to aggregation in dissolved or dispersed form and the peptides are present in the form of their acetate salts. Further, Bauer discloses that the administration of pharmaceutically active peptides is the parenteral pharmaceutical form...in the form of reconstituted lyophilisates of soluble peptide salts and to microparticles, microcapsules or implants (see paragraph [0010])...and the pharmaceutical administration forms contain peptides prone to aggregation in dissolved or dispersed form, wherein the peptides are present in the form of their acetate and other salts and these administration forms can additionally contain one of the acids as free acids (see paragraph [0011]). Bauer discloses that area of use of the preparations is in the prevention and therapy of all sex hormone-dependent conditions and diseases. Furthermore, both prior arts teach pharmaceutical gel formulation incorporating GnRH antagonist. There is a motivation to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist and one would expect the same activity. In regards to Applicant's argument that Bauer et al does not actually disclose or suggest D-63153. U.S. Patent No. 5,942,493 and DE 19911771.3 references disclose a large number of peptides, one of which is D-63153. However, Bauer et al or these references fail to provide any specific motivation to select D-63153 for use as presently claimed."

As indicated above in the body of the rejection, U.S. Patent No. 7,005,418 indicates that

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the antagonist can also be the LHRH antagonist D-63153 as described in the German Patent Application No. 199 11 771.3 (see column 3, lines 53-57). A large number of peptide antagonists is provided and known in the art. The one of ordinary skill in the art can pick and choose any known antagonist. The KSR states the following: It has been held that under KSR that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in KSR, When there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, \_\_, 82 USPQ2d 1385, 1397 (2007).

The "problem" facing those in the art was developing a sustained release formulation comprising GnRH antagonist, and there were a limited number of peptide antagonists and methodologies available to do so, for example Cetrorelix, teverelix, abarelix, ganirelix, azaline B, antide, detriorelix, ramorelix, degarelix, D-63153, Nal-Glu, antarelix etc. Geffer teaches GnRH antagonist reconstituted in 0.9% NaCl for clinical studies. The skilled artisan would have had reason to try any GnRH antagonist and methodologies with the reasonable expectation that at least one would be successful. The GnRH antagonists are well known in the art. Thus, pharmaceutical formulation comprising any one of GnRH antagonist in an aqueous solution of inorganic salt is a

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“the product not of innovation but of ordinary skill and common sense,” leading to the conclusion that invention is not patentable as it would have been obvious.

Additionally, since the claims do not further limit the structural attributes of the pharmaceutical gel preparation except the peptides have lengths of from 8 to 12 amino acids and since the prior arts teach the peptides having these limitations in pharmaceutical gel preparations, the prior arts are obvious over claims 1, 10, 12-14, 16-18, 25-27, 29-30, 32-37, 43-49 and 55-57.

15. Claims 38, 40-42, 58 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gefter et al (US Patent No. 6,180,608) in view of Bauer et al (US 2002/039996) as applied to claims 1, 10, 12-14, 16-18, 25-27, 29-30, 32-37, 43-49 and 55-57 above, in further view of Engel et al (US Patent No. 5,663,145).

16. The teachings of Gefter et al and Bauer et al are described, supra. The difference between the references and the instant claims is that the references do not teach a kit.

17. However, Engel et al teach substances available for treating hormone-dependent malignant diseases (see column 1, lines 6-7). Engel teaches that Cetrorelix (INN) is an antagonist for LHRH (see column 1, line 15). Engel teaches that in clinical trials, a daily dose of 10 mg showed a complete suppression of the hormone concentration to castration level (see column 1, lines 20-22). Additionally, Engel teaches the dosage regimen of the pharmaceutical composition: an initial dose with the amount of 1-60 mg in a lyophilisate ampoule or several lyophilisate ampoules; lyophilisate ampoules in a

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slow-release form with a rate of delivery of 0.1-10 mg/day for the whole period of treatment; or lyophilisate ampoules which contain the amount of active substance, which is not in a slow-release form, in an amount of 0.1-10 mg (see column 1, lines 42-54). The reference further teaches the aseptic procedures and lyophilizing the Cetrorelix solution (see column 2, lines 24-40). Furthermore, the reference teaches a kit comprising LHRH antagonist, Cetrorelix (see claims 1-3) and the method of treating a hormone-dependent condition (prostate cancer) comprising administering LHRH antagonist (Cetrorelix) (see claims 7 and 13).

18. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Gefter and Bauer and Engel because the prior arts teach the pharmaceutical formulation of GnRH antagonists in liquid form. All three prior arts teach the method of treating a hormone-dependent condition (prostate cancer) by administering a pharmaceutical composition of Cetrorelix. Bauer further discloses D-63153 as one of the peptides employed (see paragraph [0014] and see US Patent # 7005418, column 3, lines 53-58). One of ordinary skill in the art would be motivated to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist according to the prior arts, and thus, one would expect the same activity. There is a reasonable expectation of success since the Bauer and Engel teach the use of the formulation for the treatment of hormone-dependent disorder, specifically prostate cancer. Furthermore, there is a reasonable expectation of success since GnRH antagonists have similar properties, such as solubility, and are used to treat the same disorders.

***Response to Applicant's Arguments***

19. Applicant argues that Engel et al teach a kit comprising an initial dose of an LHRH antagonist and at least one maintenance dose of the same LHRH antagonist for the treatment of hormone-dependent conditions. The current invention claims related to a kit comprising an LHRH antagonist as finished preparation of the peptide compound and a solution of an inorganic salt or acetic acid salt for reconstitution. The combination of teaching of Gefter et al, Bauer et al, and of Engel et al does not lead to the inventive subject matter of the kit claimed.

20. Applicant's arguments have been considered but have not been found persuasive because all three cited prior arts teach the pharmaceutical formulation of GnRH antagonists in liquid form. Furthermore, Gefter et al teaches that the GnRH (LHRH) antagonist is in solid form (lyophilisate) and reconstituted in NaCl for clinical purposes. All three prior arts teach the method of treating a hormone-dependent condition (prostate cancer) by administering a pharmaceutical composition of Cetrorelix. Bauer further discloses D-63153 as one of the peptides employed (see paragraph [0014] and see US Patent # 7005418, column 3, lines 53-58). Since the claims do not further limit the structural attributes of the pharmaceutical gel preparation, and Engel et al teach the dosage regimen: an initial dose with the amount of 1-60 mg in a lyophilisate ampoule or several lyophilisate ampoules; lyophilisate ampoules in a slow-release form with a rate of delivery of 0.1-10 mg/day for the whole period of treatment; or lyophilisate ampoules which contain the amount of active substance, which is not in a slow-release form, in an amount of 0.1-10 mg (see column 1, lines 42-54) and furthermore, teach a



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kit comprising the LHRH antagonist. Since Engel et al teach the kit comprising dosage in lyophilisate ampoules (see claims 4-5) and in slow-releasing formulation (see claim 6), this meets the limitations of claim 48. Therefore, the prior arts combined meets the limitations of claims 38, 40-42, 58 and 60 and 1, 10, 12-14, 16-18, 25-27, 29-30, 32-37, 43-49 and 55-57.

***New Rejection-35 U.S.C. 112, 1<sup>st</sup>***

***(New Matter)***

21. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

22. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention.

The claim is drawn to "the pharmaceutical preparation of claim 1 wherein the pharmaceutical gel preparation further comprises at least one pharmaceutically active ionic peptide compound selected from the group consisting of cetrorelix, teverelix, abarelix, ganirelix, azaline B, antide, detirelix, ramorelix, degarelix or their pharmaceutically active salt and mixtures thereof. The claim in question recites a

“preparation further comprising at least one pharmaceutically active ionic peptide compound”.

***Lack of Ipsis Verbis Support***

23. The specification is void of any literal support for the “further comprising at least one pharmaceutically active ionic peptide compound” claimed. In the context of “further comprising”, the formulation of a pharmaceutical gel preparation comprising a mixture of D-63153 and another pharmaceutically active ionic peptide compound is not found in the specification. The examples and formulations comprising D-63153 and another pharmaceutically active ionic peptide were searched throughout the specification, however, the formulations were not found in the context of D-63153 and another pharmaceutically active ionic peptide compound anywhere in the specification. Applicant indicates that page 5, lines 17-19 of the specification supports the amendment of claim 10. However, specification page 5, lines 17-19 discloses a pharmaceutical preparation wherein the pharmaceutically active ionic peptide compound is D-63153, and the inorganic salt or the acetic salt is sodium chloride, calcium chloride, magnesium chloride, sodium acetate, calcium acetate and magnesium acetate. There is no support for the additional pharmaceutically active ionic peptide of claim 10 in the gel preparation in addition to D-63153.

***Lack of Implicit or Inherent Support***

24. “While there is not in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure.” See MPEP 2163. Thus support can be furnished implicitly or inherently for a specifically claimed limitation. However, the specification lacks any implicit or inherent support for

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the claimed “planar” substrate and “removing portions of the matrix”. As explained supra, there is no support for any concept of “further comprising additional pharmaceutically active ionic peptide compound” in the specification. Additionally, there are no examples that state that the pharmaceutical gel preparation comprising D-63153 had additional pharmaceutically active ionic peptide compound. Example 1 describes D-63153 dissolved in 30% acetic acid and mannitol addition; the solution is sterilized by filtration and lyophilized and reconstituted in sodium chloride solution. Example 2 describes lyophilized D-63153 reconstitution in water or NaCl, and the single does injection s.c. into beagle dogs. Example 3 describes D-63153 injection i.m. into male rats. Examples 4-6 describe that lyophilizates of D-63153 being reconstituted in water or NaCl. Example 7 describes lyophilizates being produced and reconstituted in NaCl solution, and administered s.c. to dogs. There is no support for the additional pharmaceutically active ionic peptide compound in the gel preparation in addition to D-63153.

### ***Conclusion***

25. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982.

The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/J. H./  
Examiner, Art Unit 1654

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